PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference C1-A0508P	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/JP2006/311600	International filing date *(day/month/year)* 09 June 2006 (09.06.2006)	Priority date *(day/month/year)* 10 June 2005 (10.06.2005)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant CHUGAI SEIYAKU KABUSHIKI KAISHA		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 11 December 2007 (11.12.2007)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yoshiko Kuwahara e-mail: pt07.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)*
Applicant's or agent's file reference C1-A0508P	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2006/311600	09.06.2006	10.06.2005

International Patent Classification (IPC) or both national classification and IPC

A61K39/395(2006.01)i, A61K9/19(2006.01)i, A61K47/02(2006.01)i, A61K47/10(2006.01)i, A61K47/18(2006.01)i, A61K47/22(2006.01)i,

Applicant

CHUGAI SEIYAKU KABUSHIKI KAISHA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP	Date of completion of this opinion	Authorized officer
Facsimile No.		Telephone No.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2006/311600

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ the translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rule 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☒ in electronic form

c. time of filing/furnishing

☒ contained in the international application as filed

☐ filed together with the international application in electronic form

☐ furnished subsequently to this Authority for the purposes of search

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/JP2006/311600

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

A. The subject matters of claims (1-6, 10, 12-19, 23, 24, 36-42 (respectively partially), 9 and 22) relate to a pharmaceutical composition containing salt and sc(Fv)2.
B. The subject matters of claims (1-6, 10, 12-19, 23, 24 and 36-42 (respectively partially)) relate to a pharmaceutical composition containing amino sugar and sc(Fv)2.
C. The subject matters of claims (1-6, 10, 12-19, 23, 24 and 36-42 (respectively partially)) relate to a pharmaceutical composition containing sugar alcohol and sc(Fv)2.
D. The subject matters of claims (1-6, 10, 12-19, 23, 24 and 36-42 (respectively partially)) relate to a pharmaceutical composition containing an amino acid and sc(Fv)2.
E. The subject matters of claims (1-6, 10, 12-19, 23, 24, 36-42 (respectively partially), 7, 8, 20 and 21) relate to a pharmaceutical composition containing a pH adjusting agent and sc(Fv)2.
F. The subject matters of claims (12, 36 (partially), 11, and 25) relate to a freeze-dried preparation containing sc(Fv)2.
G. The subject matters of claims (26-35) relate to a method for suppressing isomerization of an active ingredient in a pharmaceutical composition.
H. The subject matter of claim (43) relates to a method for screening substances which suppress isomerization of sc(Fv)2.

The pharmaceutical composition containing sc(Fv)2, which is common to A and B-F, is publicly known, for example, as described in the document ("Treatment of human B cell lymphoma xenografts with a CD3 × CD19 diabody and T cells," (B. Cochlovius), Journal of immunology, 2000, Vol. 165, No. 2, pages 888 to 895).

The pharmaceutical composition which is a matter common to A and G is publicly known without mentioning the document.

Therefore, these common matters are not considered to be special technical features, since they are within the prior art. Moreover, there is no other matter that is common to all the claims and considered to be any special technical feature.

H is neither a method for producing substances which suppress an isomerization reaction of sc(Fv)2 such as an amino sugar nor a method for using the substances. Moreover, H does not give any suggestion regarding a specified structure of compounds required for suppressing isomerization of sc(Fv)2. Accordingly, there is no single general inventive concept in A and H.

Therefore, the number of inventions included in the application concerned is eight.

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☐ all parts

   ☒ the parts relating to claims Nos. 1-6, 10, 12-19, 23, 24, 36-42 (respectively partially), 9 and 22

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	10, 12, 13, 23, 24 and 36-42 (respectively partially)	YES
	Claims	1-6, 14-19(respectively partially), 9 and 22	NO
Inventive step (IS)	Claims	12, 13, 23, 24 and 36-42(respectively partially)	YES
	Claims	1-6, 10, 14-19(respectively partially), 9 and 22	NO
Industrial applicability (IA)	Claims	1-6, 10, 12-19, 23, 24, 36-42(respectively partially), 9 and 22	YES
	Claims		NO

2. Citations and explanations:

Document 1: "Treatment of human B cell lymphoma xenografts with a CD3 × CD19 diabody and T cells," (B. Cochlovius), Journal of immunology, 2000, Vol. 165, No. 2, pages 888 to 895
Document 2: WO, 2004-019966, A1 (Chugai Seiyaku K.K.), 11 March, 2003 (11.03.04), & EP, 1541165, A1, & US, 2006-058511, A1
Document 3: JP, 2003-515323, A (Oxford Biomedica (UK) Ltd.), 7 May, 2003 (07.05.03), & WO, 2001-36486, A2, & EP, 1242456, & US, 2003-083290, A1, & US, 2004-131591, A1, & US, 2004-265275, A1, & US, 2006-014222, A1
Document 4: JP, 2002-543822, A (Smithkline Beecham Corp., US), 24 December, 2002 (24.12.02), & WO, 2000-69462, A1, & EP, 1178829, A1

(1) The subject matters of claims 1-6, 14-19 (respectively partially) (parts containing salt), 9 and 22 do not appear to be novel or to involve an inventive step, since they are described in document 1 cited in the ISR.

Especially, document 1 describes a pharmaceutical composition where a CD3 × CD19 diabody (corresponding to sc(Fv)2) is dissolved in PBS (page 889, items "Diabody expression and purification" and "Pharmacokinetic studies").

(2) The subject matter of claim 10 (partially) (part containing salt) does not appear to involve an inventive step in view of documents 1-4 cited in the ISR.

Document 1 does not describe that a composition containing sc(Fv)2 and salt is employed as a freeze-dried preparation.
As described in documents 2-4, however, it is a well-known art to employ a pharmaceutical composition containing an antibody like scFv, etc., as a freeze-dried preparation.
Therefore, a person skilled in the art could have easily conceived of employing the pharmaceutical composition described in document 1 containing sc(Fv)2 and salt as a freeze-dried preparation.

(3) The subject matters of claims 12, 13, 23, 24 and 36-42 (respectively partially)(parts containing salt) appear to be novel and to involve an inventive step, since they are neither described nor disclosed in any of the documents cited in the ISR.

The isomerization reactions of bivalent scFv and single chain diabody, and the method for suppressing the isomerization reactions described in claims 12, 13, 23, 24 and 36-42 (respectively partially) (parts containing salt), are neither described in any of the documents cited in the ISR or the documents related to the present invention, nor obvious to a person skilled in the art.

WRITTEN OPINION OF THE
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Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2006/311600

Box No. VI Certain documents cited

1. Certain published documents (Rule 43*bis*.1 and 70.10)

Application No. Patent No.	Publication date (day/*month*/year)	Filing date (day/*month*/year)	Priority date (valid claim) (*day*/month/*year*)
WO 2005/107784 A1 [P, X]	17.11.2005	11.05.2005	11.05.2004

2. Non-written disclosures (Rule 43*bis*.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/*month*/year)	Date of written disclosure referring to non-written disclosure (*day*/month/*year*)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Int.Cl.

A61K47/26(2006.01)i, A61K47/46(2006.01)i,
A61P43/00(2006.01)i, G01N33/15(2006.01)i,
G01N33/50(2006.01)i